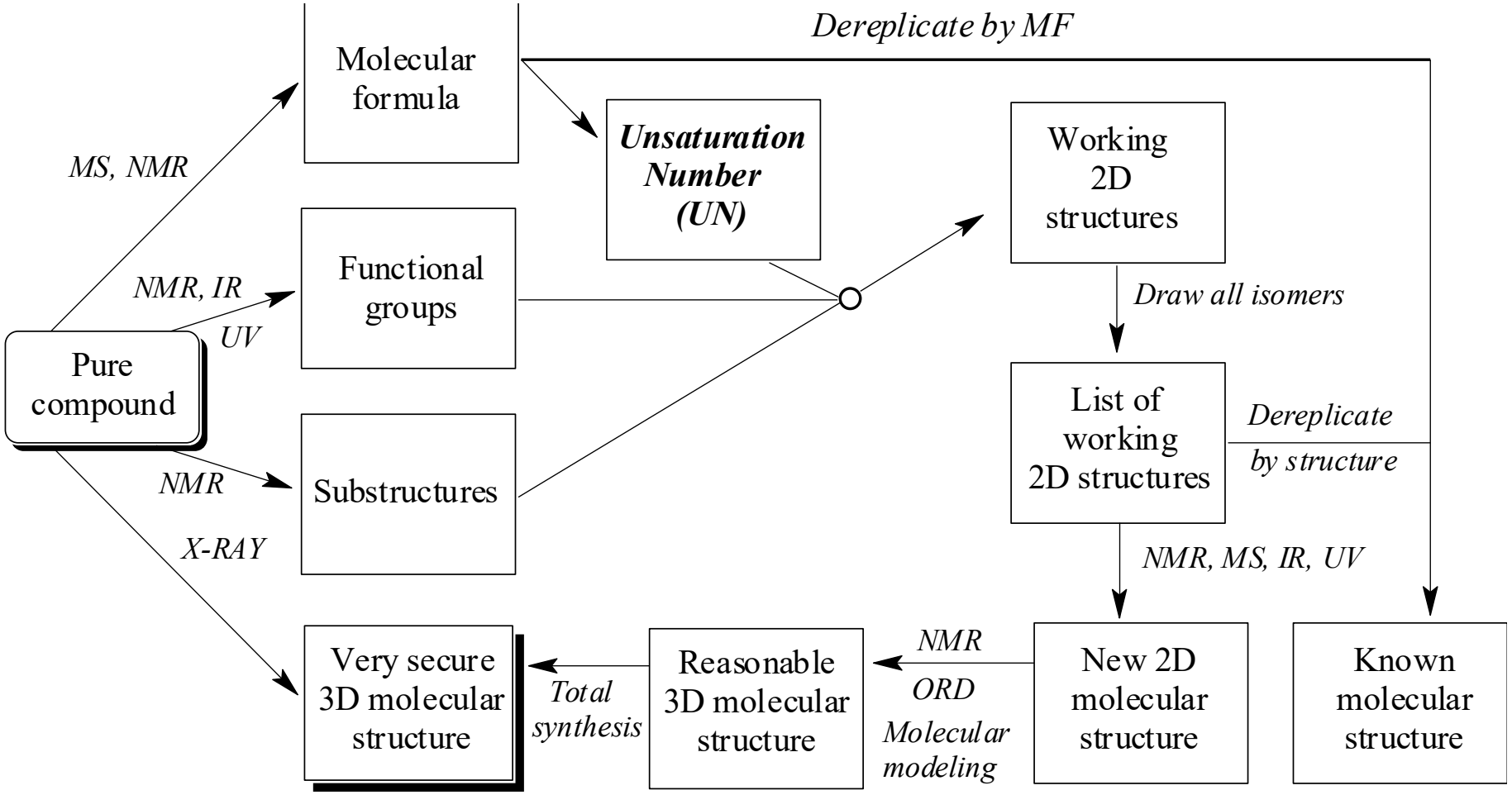
Strategy for Structure Determination

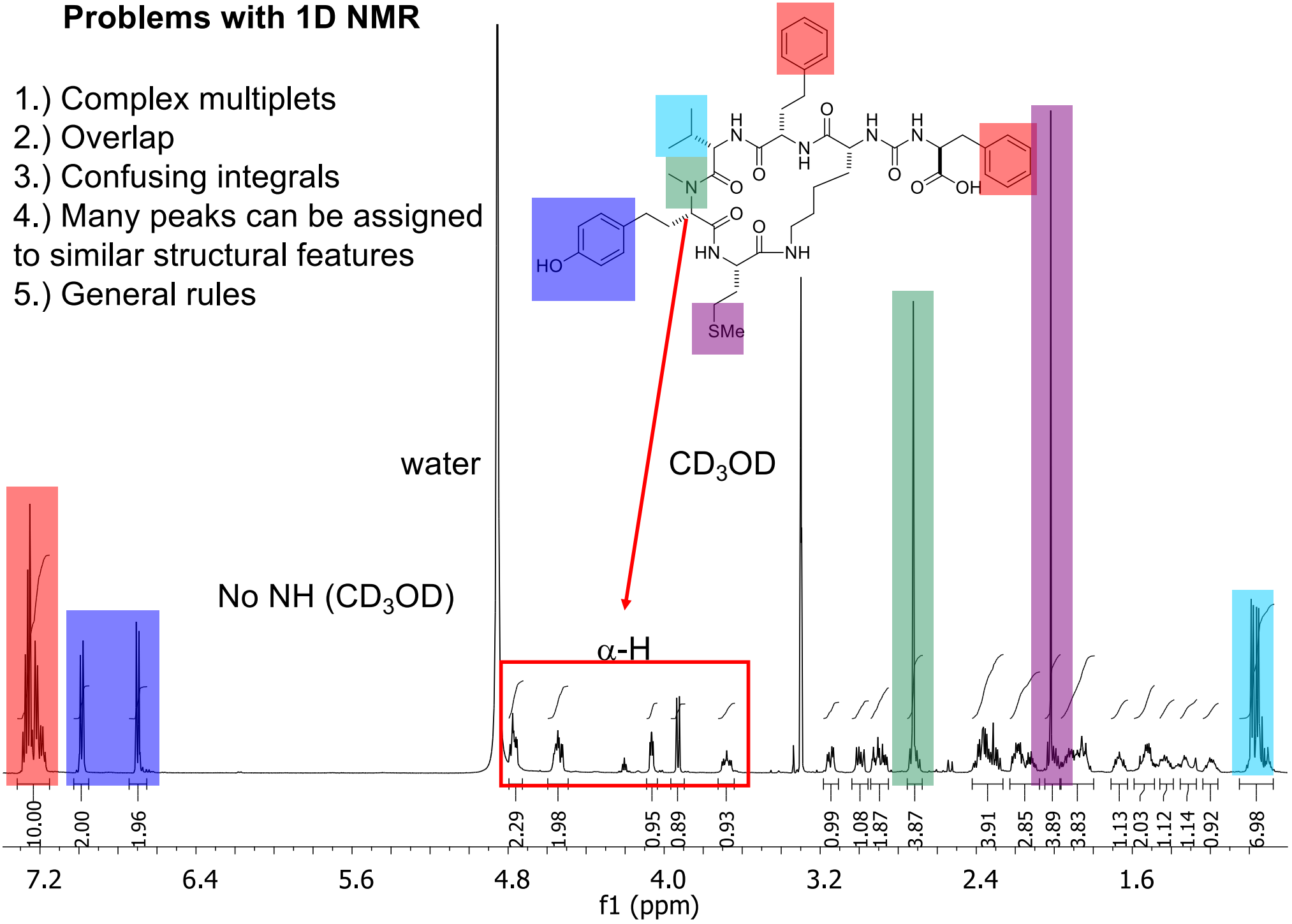
Marcel Jaspars

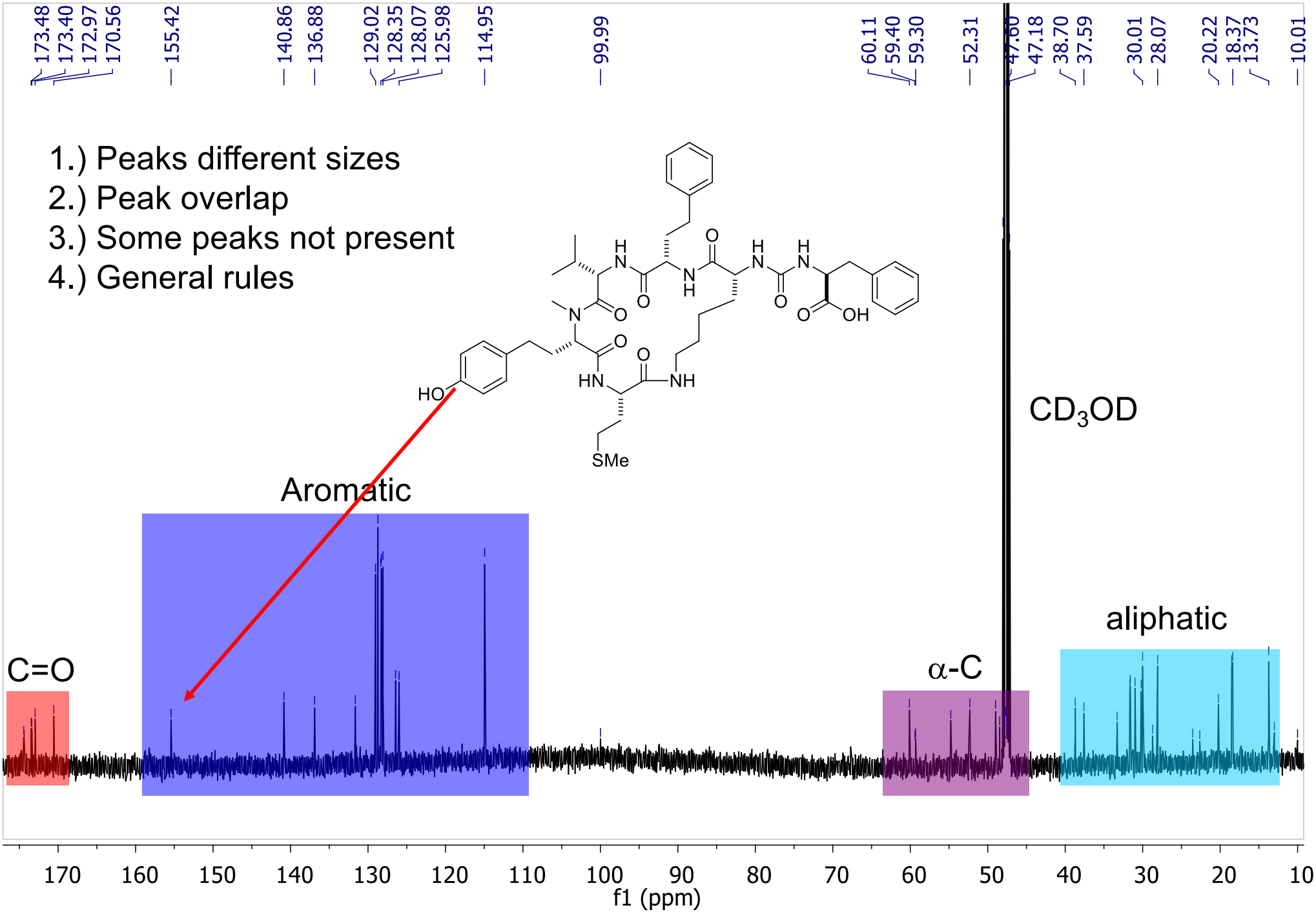
Structure Determination Steps



Problems with 1D NMR

1.) Complex multiplets
2.) Overlap
3.) Confusing integrals
4.) Many peaks can be assigned to similar structural features
5.) General rules

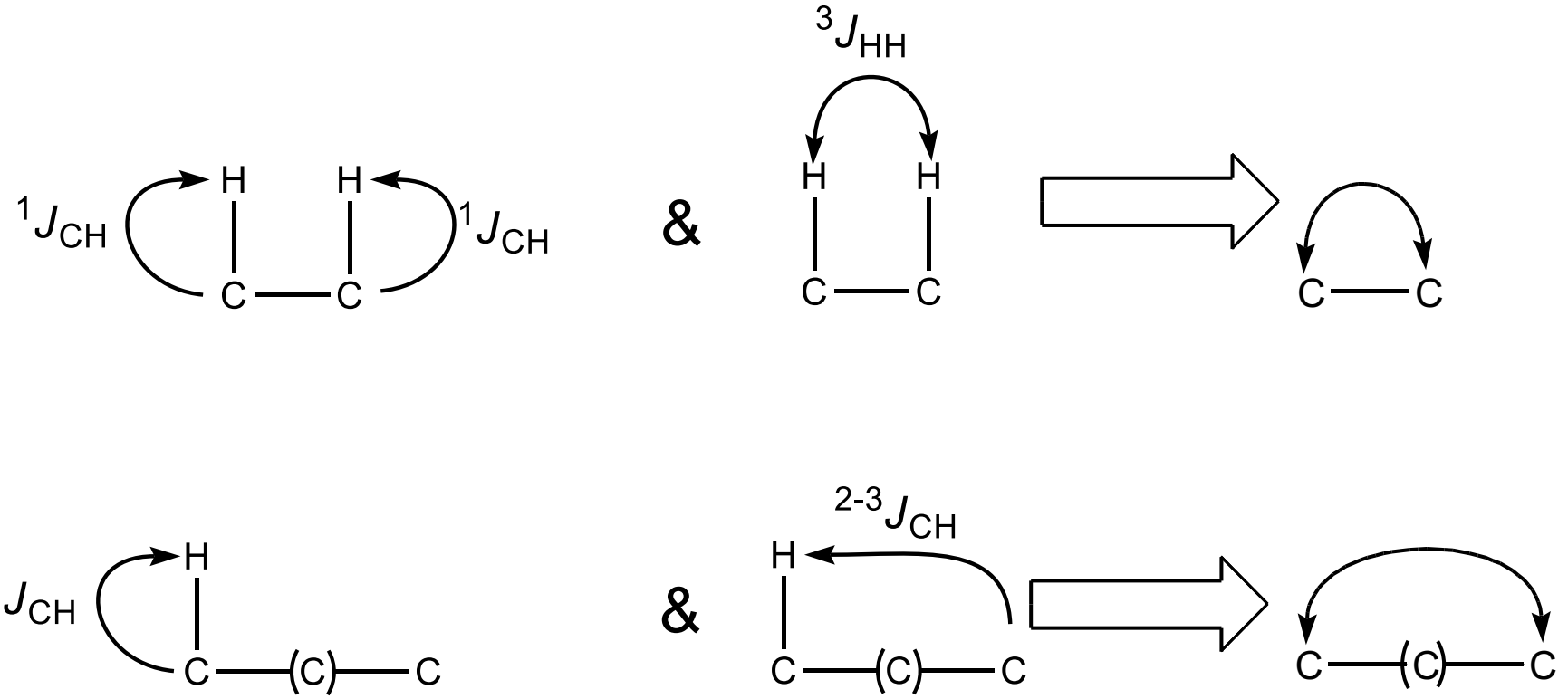



173.48
173.40
172.97
170.56
155.42
140.86
136.88
129.02
128.35
128.07
125.98
114.95
99.99
60.11
59.40
59.30
52.31
47.60
47.18
38.70
37.59
30.01
28.07
20.22
18.37
13.73
10.01
1.) Peaks different sizes
2.) Peak overlap
3.) Some peaks not present
4.) General rules
HO
HN
NH
SMe
OH
CD3OD
Aromatic
C=O
α-C
aliphatic
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

The 2nd Dimension

- For complex molecules a great deal of overlap occurs in the ^{1}H, and sometimes ^{13}C NMR spectra.
- Many ^{1}H-^{1}H coupling constants will be the same or similar making it difficult to determine connectivity.
- Need alternative approach that gives connectivities without analysing coupling constants.
- Can do this by introducing a second NMR dimension correlating ^{1}H with ^{1}H or ^{1}H with ^{13}C.

Strategy Based on C-H Connectivity



Structure Determination Steps

MF = $C_{10}H_{18}O$

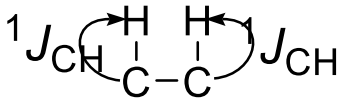
sp^3: Me Me Me

sp^3: CH_2 CH_2 CH_2

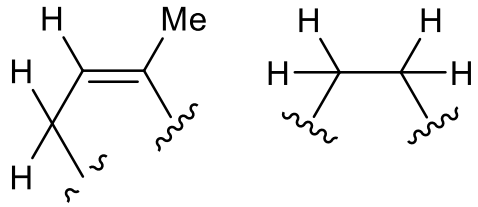
sp^3: CH; sp^2: CH

sp^3: C-OH; sp^2: C

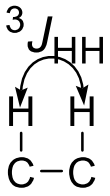
1.) Obtain C/H pairs from HSQC

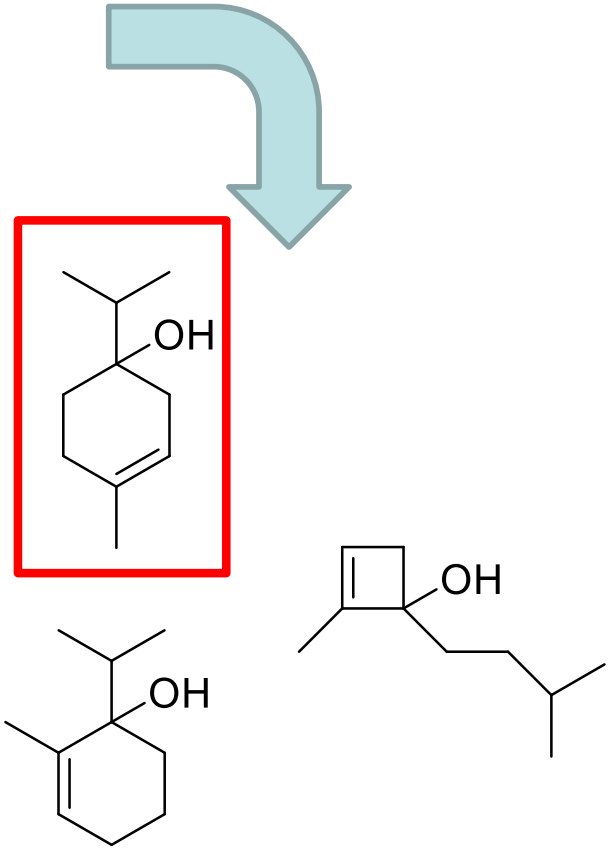


2.) Determine functional groups (NMR, IR etc)

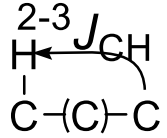


3.) Generate substructures



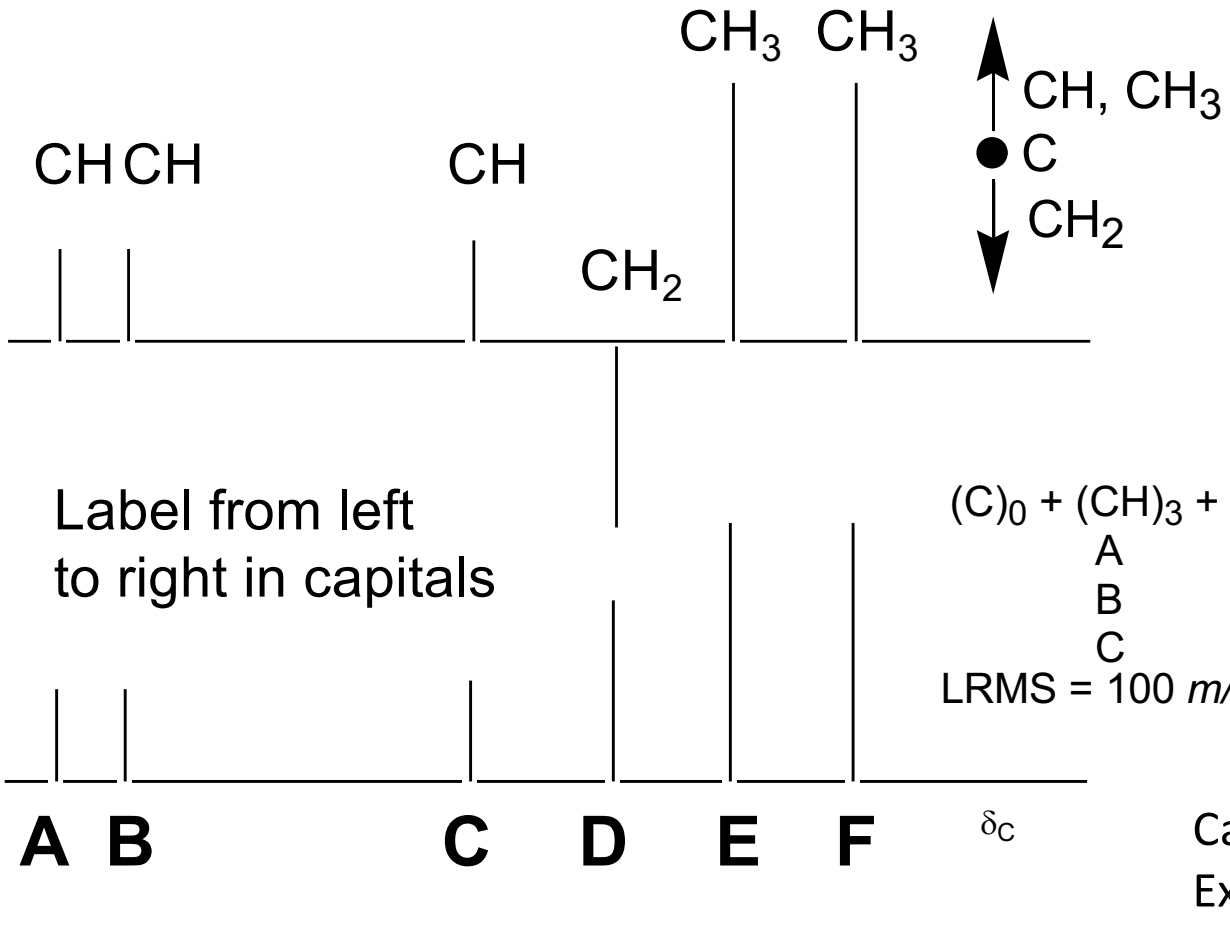


4.) Assemble working structures



5.) Make structural proposal

Strategy Based On C-H Connectivity – DEPT Data



$(C)_0 + (CH)_3 + (CH_2)_1 + (CH_3)_2 = C_6H_{11} = 83$

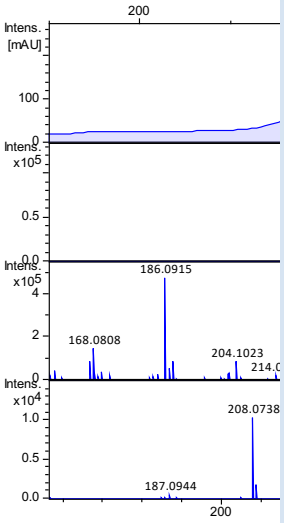
A D E
B F
C

LRMS = 100 *m/z* so add OH MF = $C_6H_{12}O$

Calc Mass = 100.0888

Exp Mass = 100.0879

Determining the MF



SmartFormula Manually

Lower formula:

Upper formula:

Generate

Help

Note: for m < 2000 the elements C, H, N, and O are considered implicitly.

Adducts, pos. M+H Collect adducts

Adducts, neg. M-H

Measured m/z 277.119 Tolerance: 4 mDa Charge: 1

Meas. m/z	#	Ion Formula	m/z	err [ppm]	mSigma	# mSigma	Score	rdb	e⁻ Conf	N-Rule
277.1190	2	$C_{14}H_{17}N_2O_4$	277.1183	-2.5	9.5	2	100.00	8.0	even	ok
277.1190	3	$C_{15}H_{13}N_6$	277.1196	2.4	23.1	3	76.66	13.0	even	ok
277.1190	1	$C_{10}H_{13}N_8O_2$	277.1156	-12.1	9.2	1	12.68	9.0	even	ok
277.1190	4	$C_{19}H_{17}O_2$	277.1223	12.1	35.3	4	7.29	12.0	even	ok

Automatically locate monoisotopic peak Maximum number of formulae 500

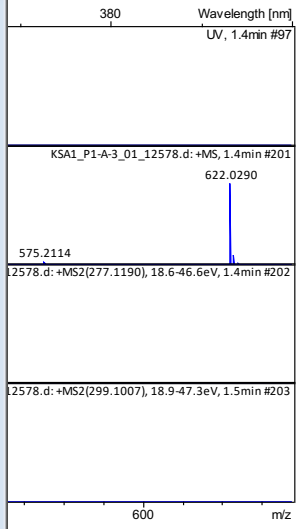
Check rings plus double bonds Minimum -0.5 Maximum 40

Electron configuration even

Filter H/C element ratio Minimum H/C: 0 Maximum H/C: 3

Estimate carbon number Generate immediately

Copy to SmartFormula Parameters Show Pattern



Data:
Kojo
Acquah

Double Bond Equivalents/Unsaturation Number

- Sum of number of double bonds and rings
- C=C, C=O etc. counts as 1 double bond, C≡N counts as 2, benzene ring as 4 (3 double bonds + 1 ring)

$$C_aH_bO_cN_dX_e$$

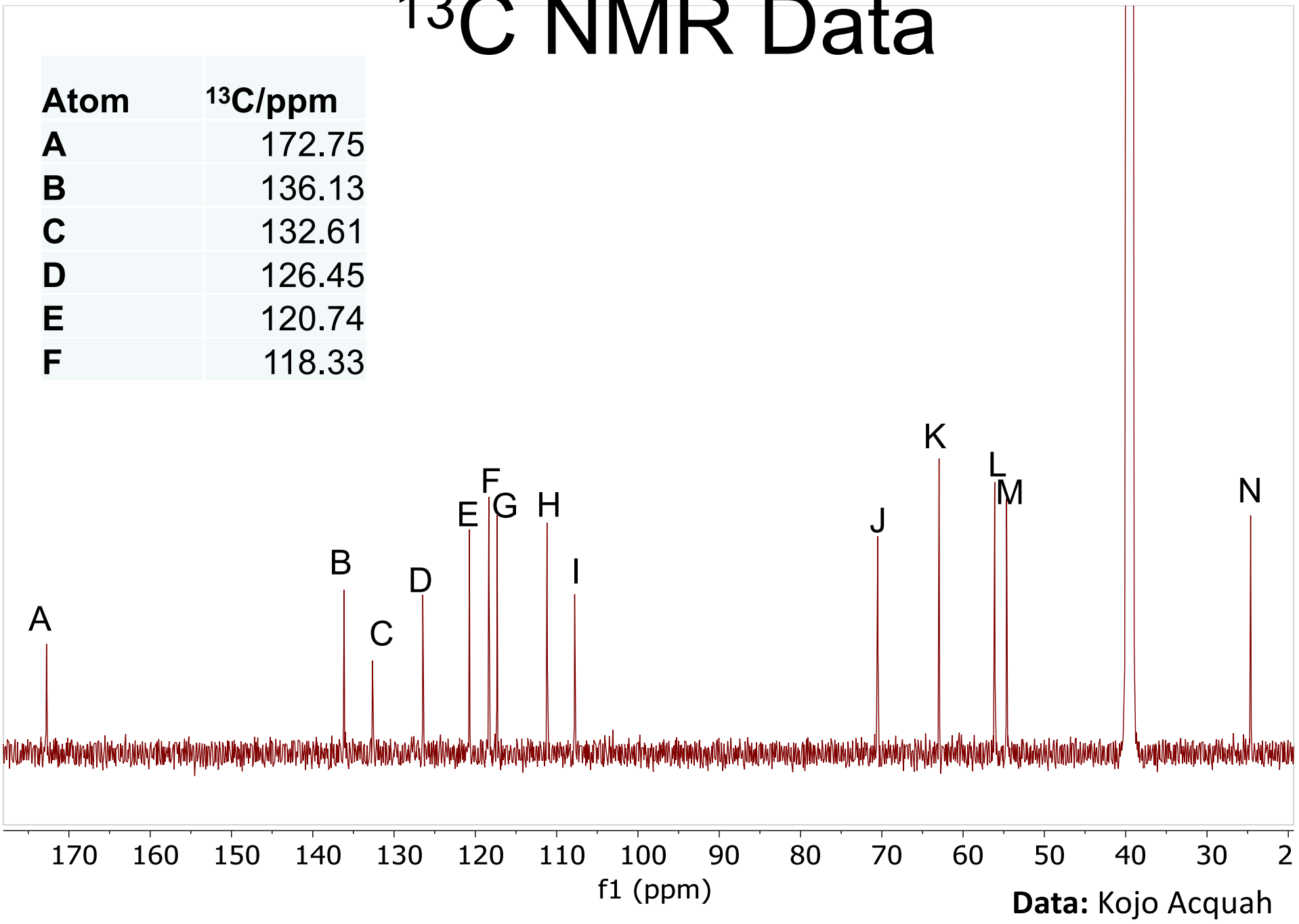
$$DBE = \frac{[(2a+2) - (b-d+e)]}{2}$$

$C_2H_3O_2Cl$ =

Calculate it for: $C_{14}H_{16}N_2O_4$

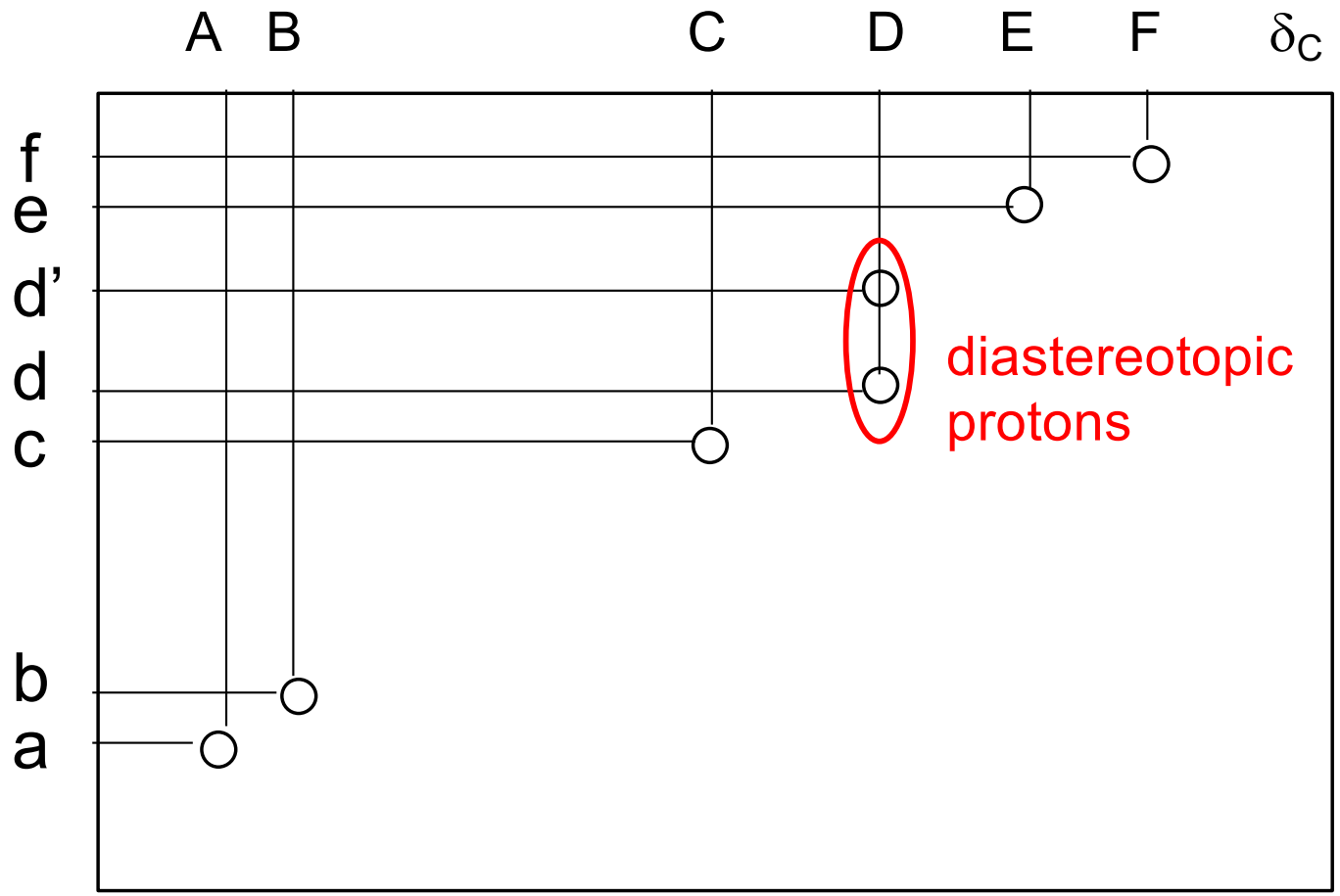
^{13}C NMR Data

Atom	^{13}C/ppm
A	172.75
B	136.13
C	132.61
D	126.45
E	120.74
F	118.33



Data: Kojo Acquah

Strategy Based On C-H Connectivity – HSQC Data



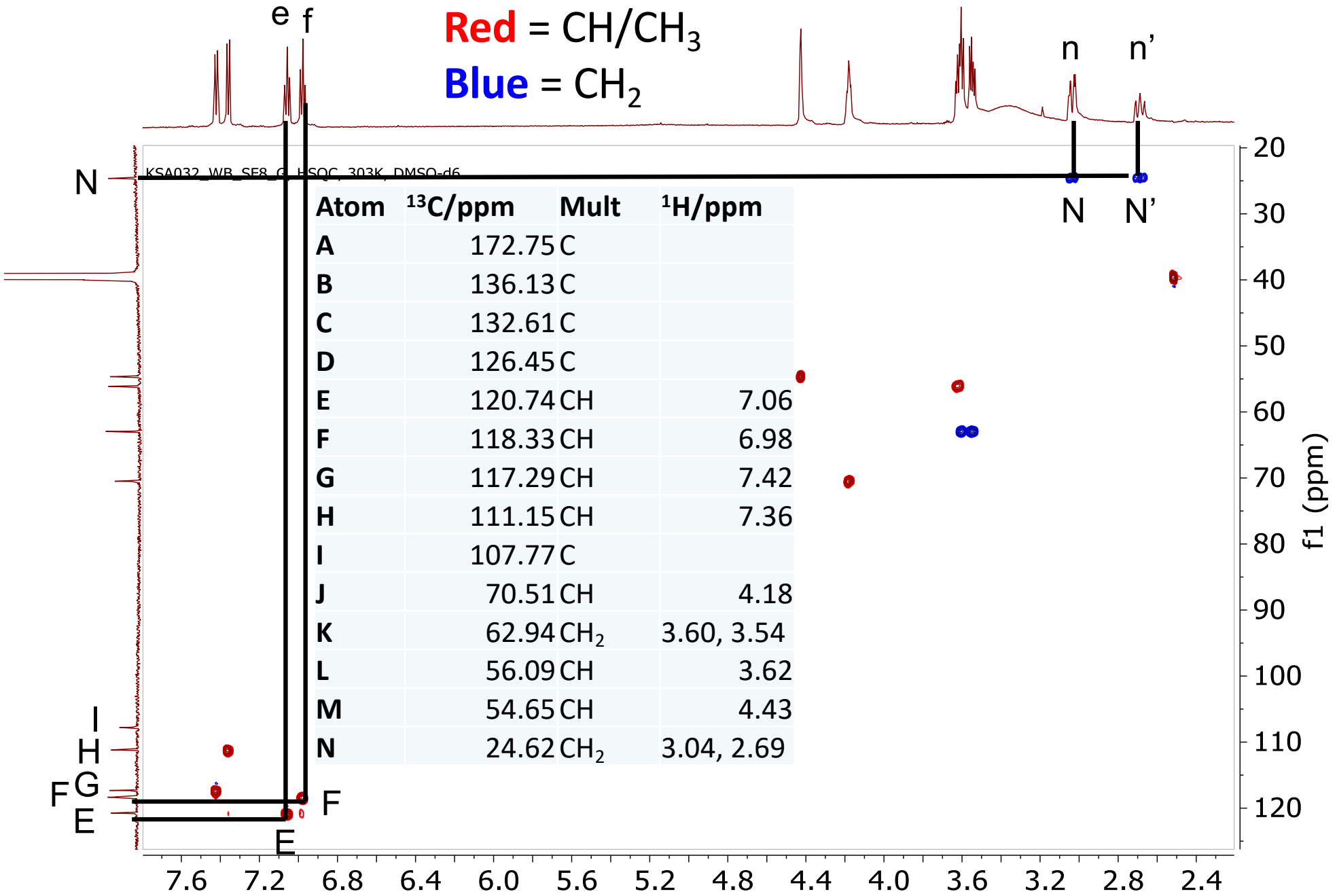
label protons in lower case letters

$^1J_{CH}$ = 140 Hz; C-H direct correlations (1 bond)

HSQC Data - C-H (1 bond)

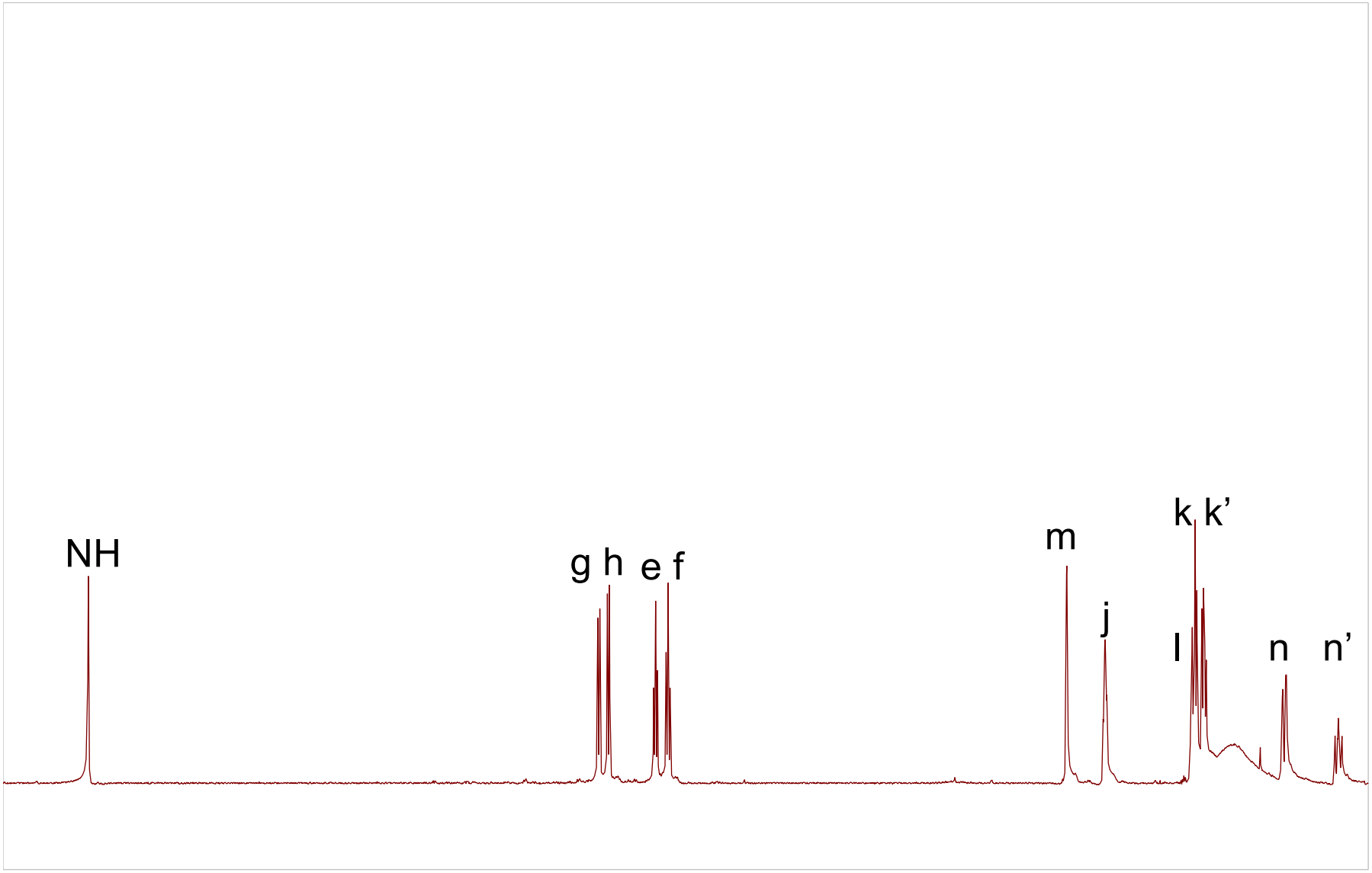
Red = CH/CH_3

Blue = CH_2



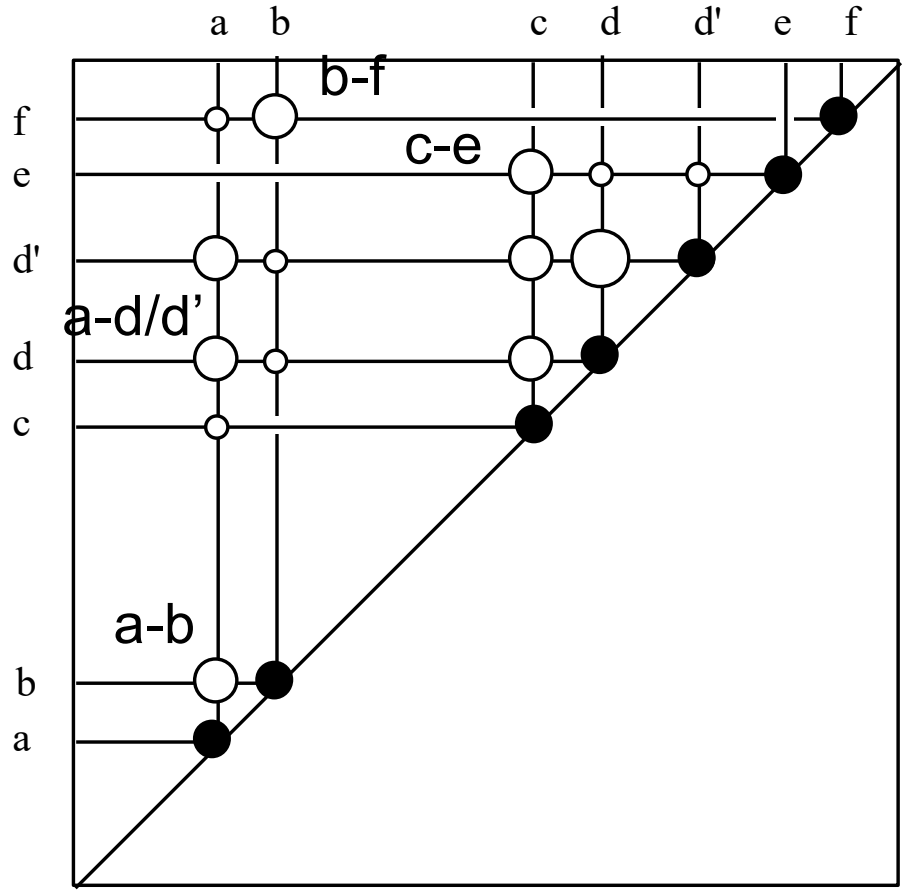
Atom	^{13}C/ppm	Mult	^{1}H/ppm
A	172.75	C	
B	136.13	C	
C	132.61	C	
D	126.45	C	
E	120.74	CH	7.06
F	118.33	CH	6.98
G	117.29	CH	7.42
H	111.15	CH	7.36
I	107.77	C	
J	70.51	CH	4.18
K	62.94	CH_2	3.60, 3.54
L	56.09	CH	3.62
M	54.65	CH	4.43
N	24.62	CH_2	3.04, 2.69

^{1}H NMR Data



Data: Kojo Acquah

Strategy Based On C-H Connectivity – COSY Data



Geminal (2 bond)

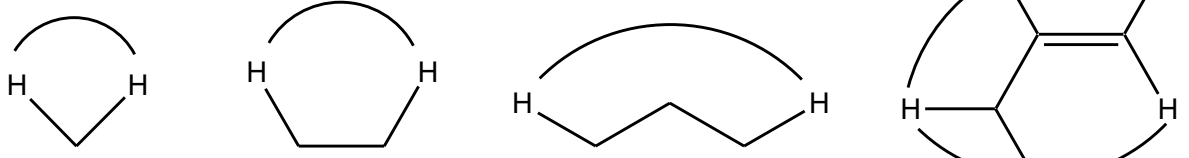
Vicinal (3 bond)

4 bond

Diagonal

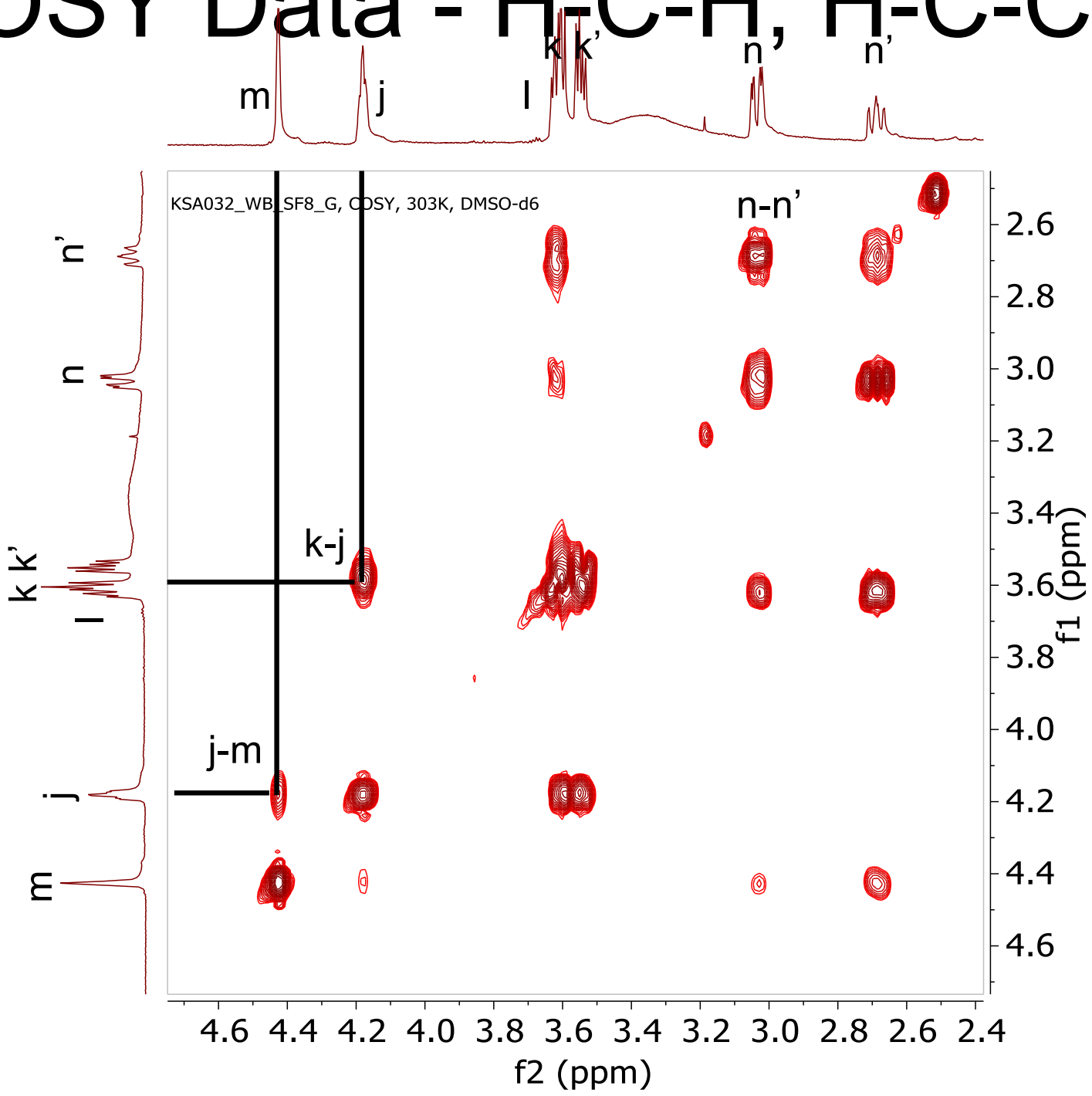
And many more…

$^{2}J_{HH}$ $^{3}J_{HH}$ $^{4}J_{HH}$



allylic

COSY Data - H-C-H, H-C-C-H

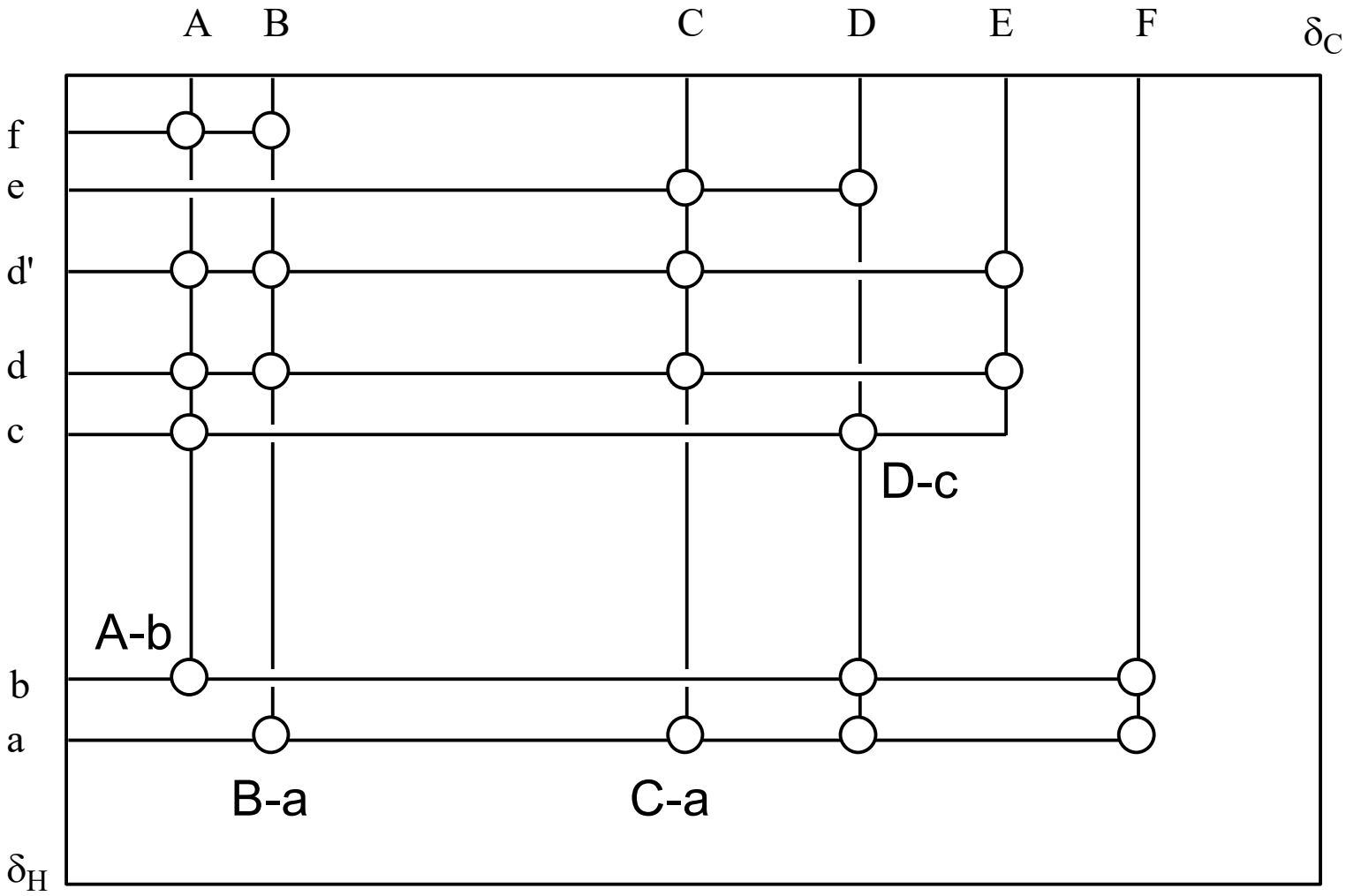


COSY Data - H-C-H, H-C-C-H

Atom	^{13}C/ppm	Mult	^{1}H	COSY
A	172.75	C		
B	136.13	C		
C	132.61	C		
D	126.45	C		
E	120.74	CH	7.06	f, h
F	118.33	CH	6.98	e, g
G	117.29	CH	7.42	f
H	111.15	CH	7.36	e
I	107.77	C		
J	70.51	CH	4.18	m, k
K	62.94	CH_2	3.60, 3.54	j
L	56.09	CH	3.62	n
M	54.65	CH	4.43	j, n
N	24.62	CH_2	3.04, 2.69	l, m

Data: Kojo Acquah

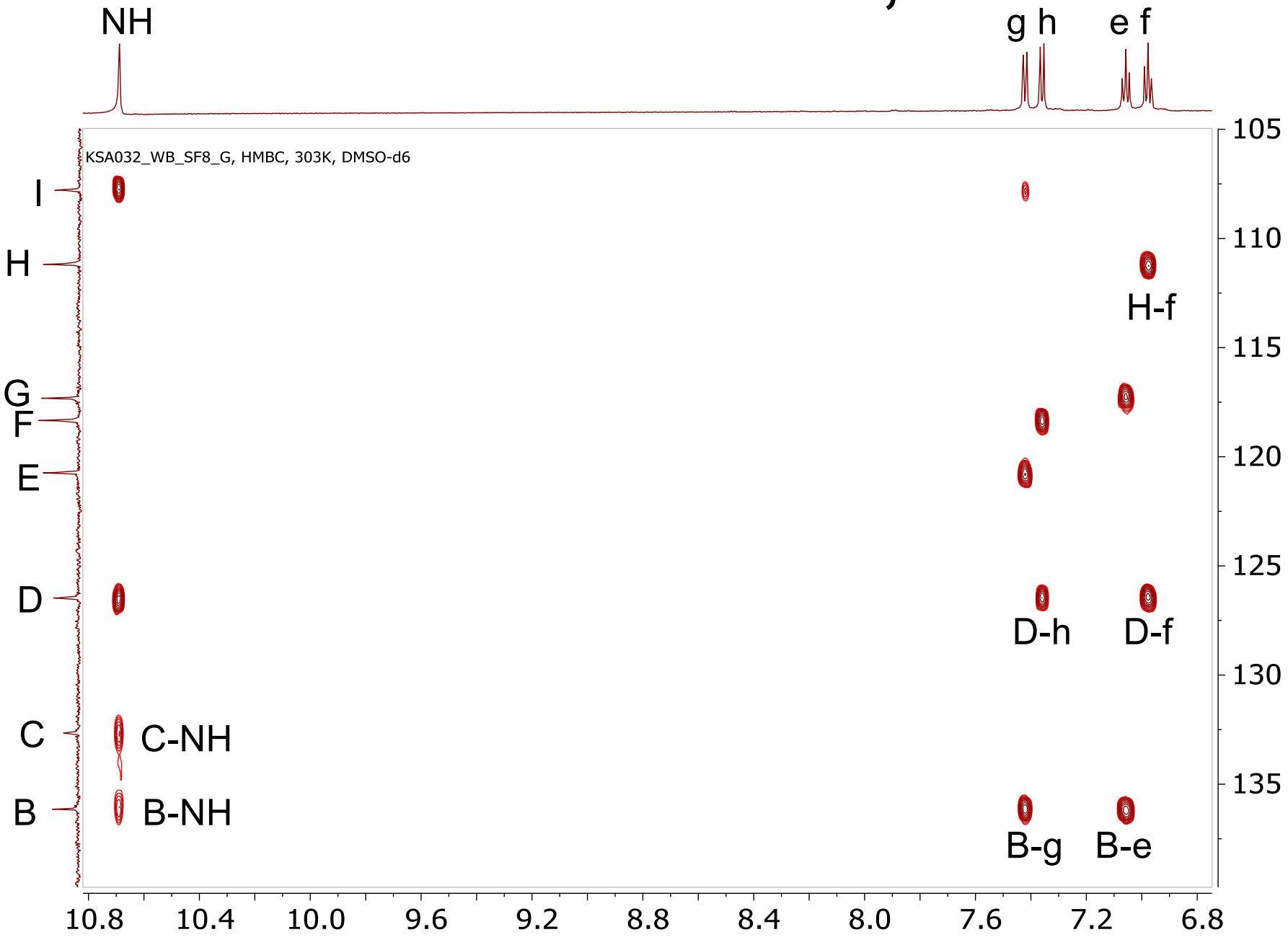
Strategy Based On C-H Connectivity – HMBC Data



And many more…

$^{2\text{-}3}J_{CH}$ = 9 Hz; C-H indirect (long range) correlations
(2-3 bonds) C-C-H & C-C-C-H

HMBC Data - C-C-H, C-C-C-H



HMBC Data - C-C-H, C-C-C-H

Atom	^{13}C/ppm	Mult	^{1}H	COSY	HMBC
A	172.75	C			l, n
B	136.13	C			HN, g, e
C	132.61	C			HN, m, j, n
D	126.45	C			HN, h, f, n
E	120.74	CH	7.06	f, h	g, f
F	118.33	CH	6.98	e, g	h
G	117.29	CH	7.42	f	e,f
H	111.15	CH	7.36	e	f, g, e
I	107.77	C			HN, g, m, n
J	70.51	CH	4.18	m, k	m, k
K	62.94	CH_2	3.60, 3.54	j	j, m
L	56.09	CH	3.62	n	n
M	54.65	CH	4.43	j, n	l, k
N	24.62	CH_2	3.04, 2.69	l, m	l

Data: Kojo Acquah

Simple Example – $C_6H_{12}O$

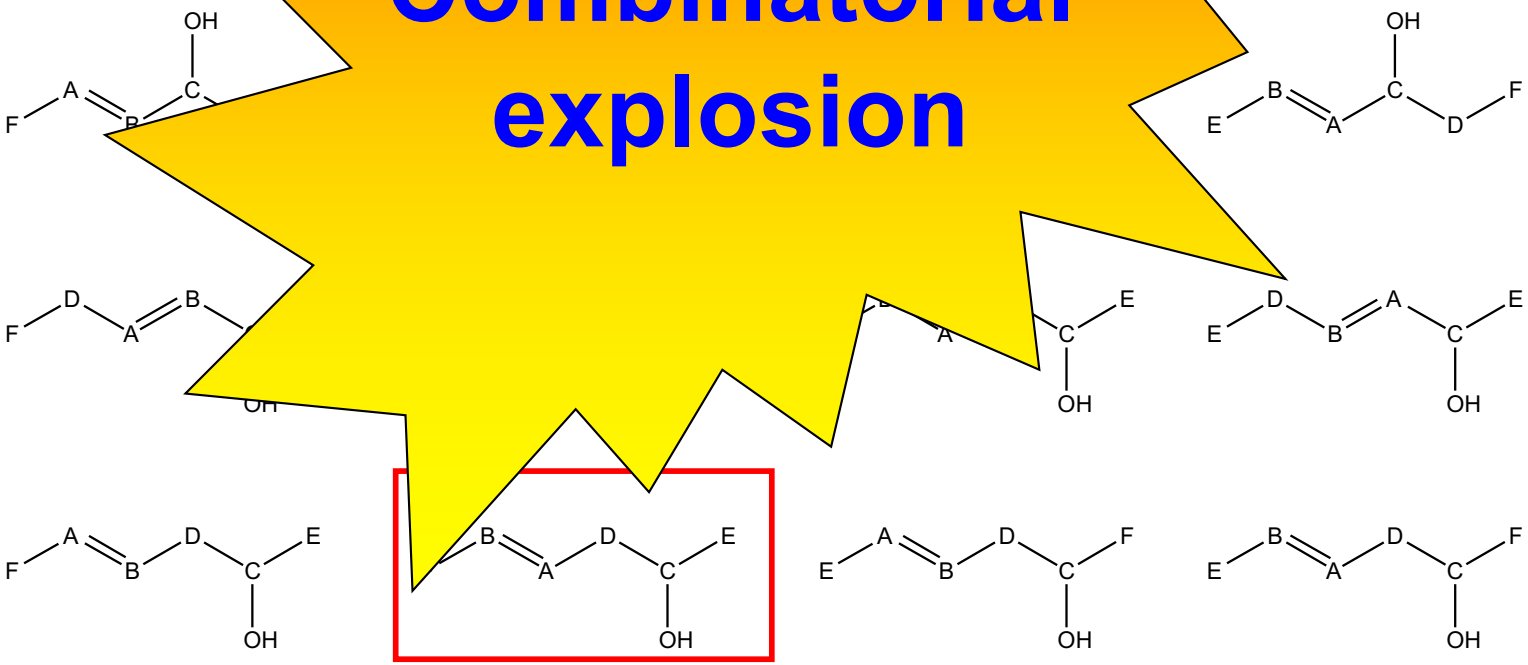
ATOM	δ_C (ppm)	DEPT	δ_H (ppm)	COSY (H→H)	HMBC (C→H)
A	131	CH	5.5	b, c, d/d', f	b, c, d, f
B	124	CH	5.2	a, d/d', f	a, d, f
C	68	CH	4.0	a, d/d', e	a, d, e
D	42	CH_2	3.0 2.5	a, b, c, d, e	a, b, c, e
E	23	CH_3	1.5	c, d/d'	c, d
F	17	CH_3	1.2	a, b	a, b

Strategy Based On C-H Connectivity
Retrospective Che king

Pieces:

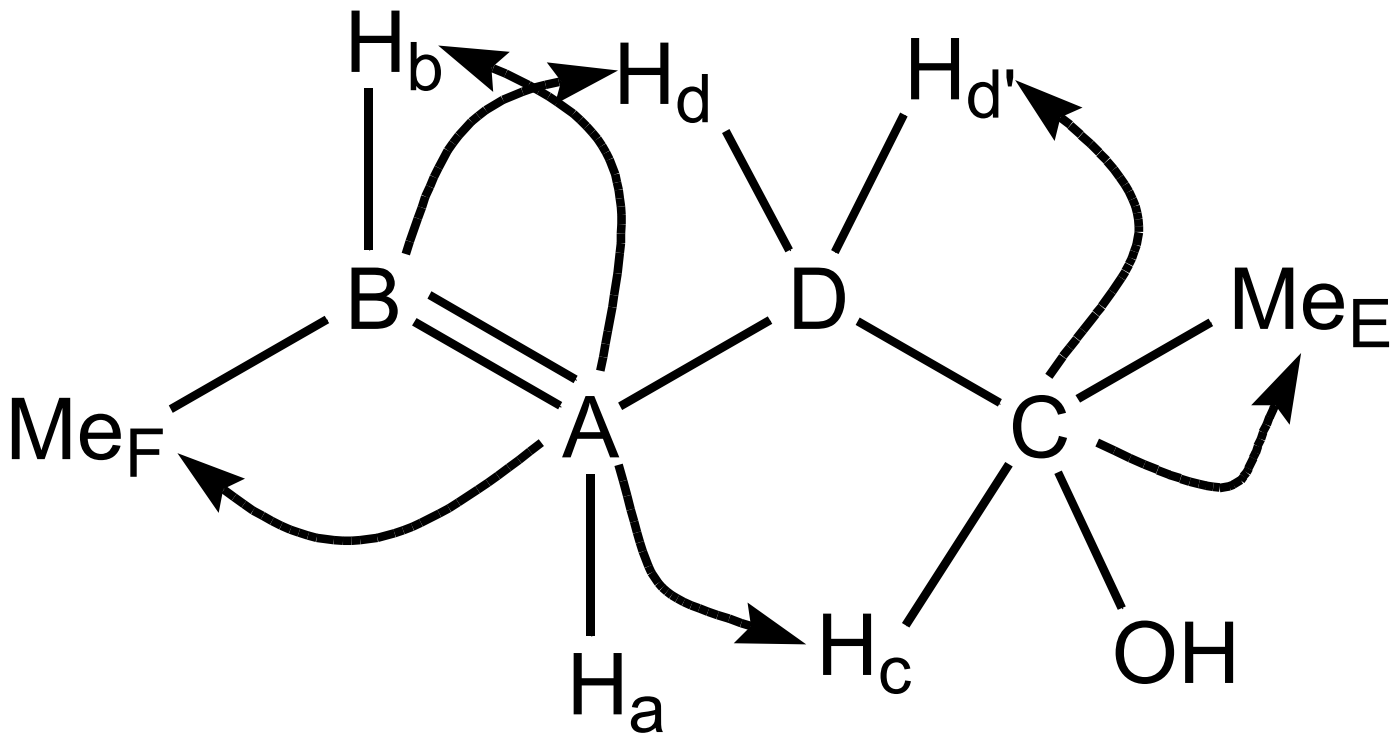
Possibilities:

Combinatorial explosion



Strategy Based On C-H Connectivity
Retrospective Checking

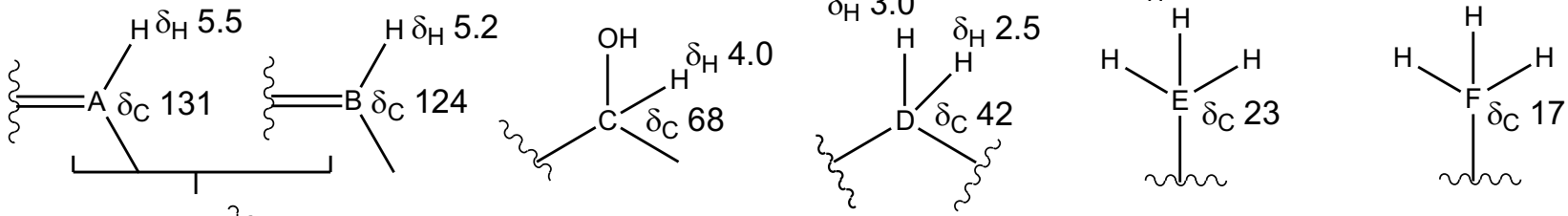
HMBC data (C-C-H & C-C-C-H) from C → H

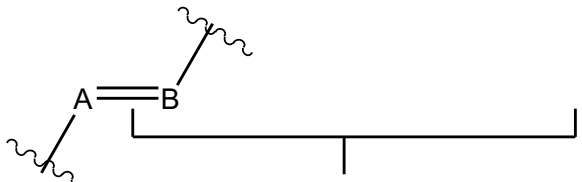


And similarly for COSY data

Prospective Checking

Pieces:

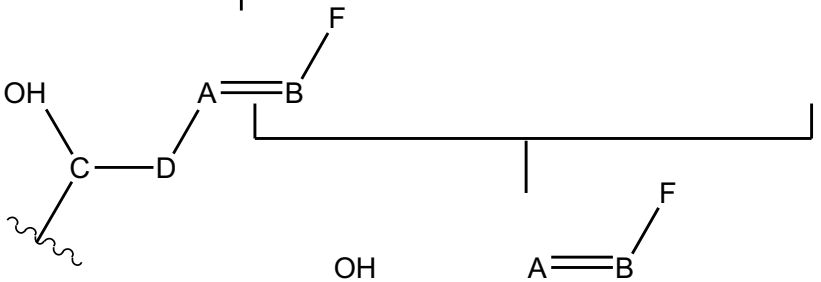




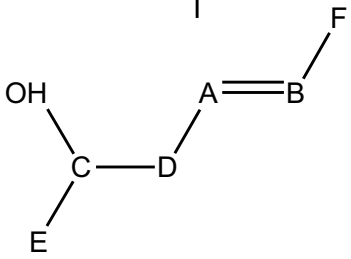
Reason: only 2 sp^2 C's

HMBC: F-a, F-b, A-f, B-f

HMBC: D-a, D-b, A-d, B-d



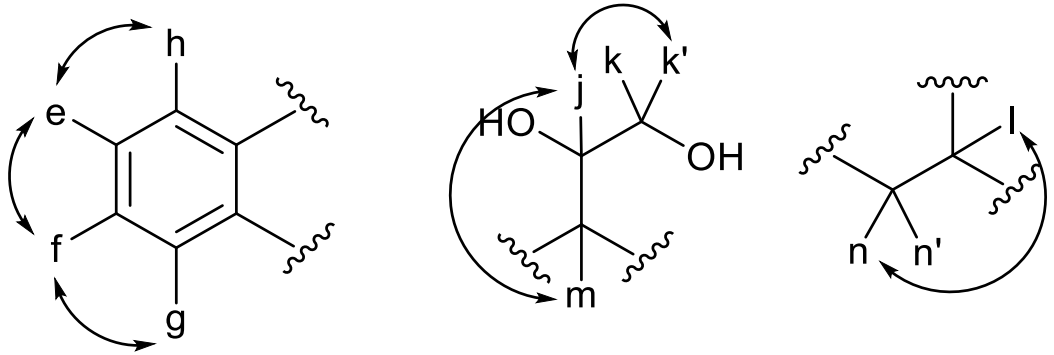
HMBC: C-d, C-a, D-c, A-c



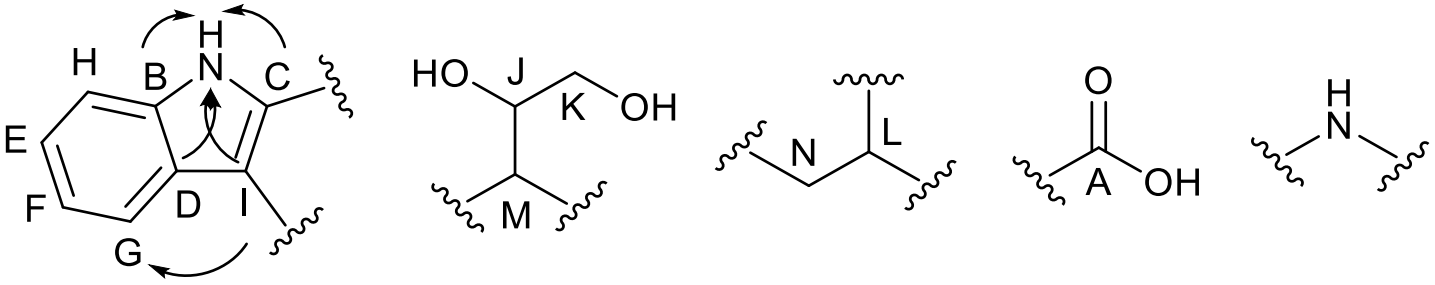
HMBC: E-c, E-d, C-e, C-d

Real Example

COSY Data



HMBC Data



$C_{14}H_{16}N_2O_4$ (DBE = 8)

Combining the Pieces